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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/913,521	Applicant(s) MATSUYAMA ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,17,21-24 and 27-32* is/are pending in the application.

4a) Of the above claim(s) *4,5,21,22 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-15,17,23,24 and 30-32* is/are rejected.

7)☒ Claim(s) *7-9,12,31 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 4/14/03, as Paper No. 17. The amendment has been entered. Claims 6, 7, 8 and 10 have been amended. New claims 30-32 have been added. Claims 3, 16, 18, 19, 20, 25 and 26 have been cancelled. Claims 1, 2, 4-15, 17, 21-24 and 27-32 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Claims 4, 5, 21, 22 and 27-29 previously set forth have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim, for the reasons of record. Applicant timely traversed the restriction (election) requirement in Paper No. 8, filed 4/1/02.

4. Claims 1, 2, 6-15, 17, 23, 24 and 30-32 are examined herein.

Claim Objections

The objections to claims 3, 6, 7 and 8-15 previously set forth have been withdrawn because the claims have been cancelled or amended to overcome the objection.

Claim Rejections – 35 USC § 112, second paragraph

5. The rejection of claims 25 and 26 under than 35 U.S.C. 112, second paragraph, as being indefinite is now moot because the claims have been cancelled.

New Grounds of Rejections/Objections

The previous Office Action indicated that claims 1, 2, 16-20, 23 and 24 appeared to be allowable as the prior art does not teach a polynucleotide comprising 0.1-3% 2'-5' phosphodiester bonds. Upon further consideration, the claims still appear to be free of the prior art; however, the claims are not allowable for the reasons set forth below.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 and 24 depend on claim 18, which has been cancelled. Therefore, claims 23 and 24 are indefinite because limitations of the claims cannot be determined.

It is noted that claims 23 and 24 were originally (and incorrectly) numbered as claims 16 and 17, both of which were dependent on incorrectly numbered claim 8. However, claims 8, 16 and 17 were renumbered under CFR 1.132 correctly as 18, 23 and 24, respectively. Furthermore,

claims 23 and 24 were adjusted to depend on correctly numbered claim 18. Claim 18 has been cancelled. Now claims 23 and 24 depend on a cancelled claim.

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 2, 6, 8-15, 17 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. The instant claims are drawn to a chain shortened polynucleotide or salt thereof comprising phosphodiester bonds wherein from about 0.1 percent to about 3 percent of the phosphodiester bonds are 2'-5' phosphodiester bonds (see claim 1). The claim is very broad and encompasses any chain shortened polynucleotide, regardless of size, sequence or base composition. Therefore, the claims encompass a genus comprising a vast number of species (i.e. polynucleotides) with the only limitation being that each member of the genus is a polynucleotides comprising from about 0.1 percent to about 3 percent 2'-5' phosphodiester bonds. However, the specification only discloses chain shortened polynucleotides (which have the desired function) that are 0.1-1.0 kilobases in length, comprise 0.1-3% 2'-5'phosphodiester

bonds, and are composed of polyinosinic acid, polycytidylic acid. Therefore, the claims encompass molecules which are not adequately described in the specification.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

The only functions for the claimed polynucleotides contemplated in the specification are therapeutic functions, such as inducing interferon production for the treatment of cancer or viral infection. The only polynucleotides described in the specification which actually have the described functions are polynucleotides that are 0.1-1.0 kilobases in length, and are composed of polyinosinic (poly-I) acid and polycytidylic (poly-C) acid. The specification only indicates that polynucleotides that are 0.1-1.0 kilobases in length, are composed of polyinosinic (poly-I) acid and polycytidylic (poly-C) acid and which comprise about 0.1% to about 3% 2'-5'phophodiester bonds have a the desired therapeutic effect and a reduced toxicity (compared to the polynucleotides which do not comprise 2'-5' bonds). The specification does not indicate that any polynucleotides other than polynucleotides 0.1-1.0 kilobases in length which comprise 0.1-3% 2'-5'phosphodiester bonds and are composed of polyinosinic acid, polycytidylic acid, would have the same therapeutic and function with reduced toxicity. There is no guidance provided which would indicate the critical structural elements that are common to all of the species and

which are responsible for their function. Without a clear indication of the structures required for the species to have the all of the desired functions (therapeutic with reduced toxicity), one of skill in the art would not know which species encompassed by claims would be functional species and which would be non-functional. Therefore, the specification does not provide an adequate written description of the polynucleotides encompassed by the claims.

11. Additionally, claims 1, 2, 6, 8-15, 17 and 32 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are very broad and encompass any polynucleotide that comprises about 0.1% to about 3% 2'-5' phosphodiester bonds; and wherein the only contemplated use for the polynucleotides is for therapeutic purposes. However, as mentioned above, the specification has not adequately described the polynucleotides encompassed by the claims. Without a clear indication of the structures required for the species to have the desired functions, one of skill in the art would not know which species encompassed by claims would be functional species and which would be non-functional.

12. Claims 1, 2, 6-15, 17 and 30-32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A chain shortened polynucleotide or salt thereof that is between 0.1 kilobases and 1 kilobases and comprises about 0.1% to 3% 2'-5' phosphodiester bonds wherein said chain shortened polynucleotide can be used as an interferon inducing agent, or an immune activating agent;

does not reasonably provide enablement for the full scope of the claims—specifically, the claims are not enabled for preventing any disease, such as cancer or hepatitis (as set forth in claim 15). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to polynucleotides which the disclosure only describes as being useful for therapeutic purposes, such as treating or **preventing** cancer or hepatitis. Therefore, the nature of the invention is therapeutic polynucleotides.

The breadth of the claims

The claims are very broad and encompass any polynucleotide that comprises about 0.1% to about 3% 2'-5' phosphodiester bonds wherein the polynucleotide can be used as a therapeutic compound. It is noted that preventing a disease encompasses permanently inhibiting any future occurrence of the disease.

Working Examples and Guidance in the Specification

The specification indicates that polynucleotides that are about 0.1 kilobases to about 1 kilobases in length and which comprise poly-I acid and poly-C acid are effective at inhibiting the growth of cancer cells. However the specification also indicates that these polynucleotides are also toxic to bone marrow cells (see p. 27, Table 6). The specification indicates that when the above mentioned polynucleotides comprise about 0.1 percent to about 3 percent 2'-5' phosphodiester bonds, and the polynucleotides exhibit a lower toxicity than polynucleotides not comprising 2'-5' phosphodiester bonds (e.g., see p. 26, Table 5; and p. 29, Table 7). The specification indicates that the growth inhibiting action was remarkably strong in a combination of chain-shortened polyinosinic acid and polycytidylic acid wherein each contained less than 3% 2'-5' phosphodiester bonds and indicates that when the rate is 3% or more, the action became weaker (see p. 29 lines 5-16); thus indicating that the therapeutic effectiveness of polynucleotide decreased as the percent 2'-5' bonds increased.

It is pointed out that the only polynucleotides which have the desired therapeutic effect in combination with the decreased toxicity are polypeptides that are about 0.1kb to about 1kb in length and are comprised of poly-I acid and poly-C acid.

The specification does not indicate that any other polynucleotides (i.e., other than poly-I and poly-C polynucleotides) will have the therapeutic effect; or that the incorporation of up to about 3% 2'-5'bonds will decrease the toxicity of any other type of polynucleotide (e.g. polyadenylic acid or polyuridylic acid). There is also no indication that any polynucleotide other than the poly-I and poly-C polynucleotides would have any therapeutic effect.

Furthermore, there is no indication in the specification that any polynucleotide would be able to prevent any future occurrence of any disease, such as cancer or hepatitis) in a subject.

The unpredictability of the art and the state of the prior art

There are no examples in the prior art which indicate that any compound can absolutely prevent any future occurrence of any disease (including cancer and hepatitis) in a subject. In fact, diseases such as cancer and hepatitis viral infection are complex diseases for which a great amount of experimentation is currently being done in order to identify therapeutic compounds for effectively treating as well as for preventing cancer and hepatitis, prima facie evidence that no absolute inhibitors have yet been identified. Furthermore, the vast amount of experimentation which has been done to identify absolute inhibitors of cancer and hepatitis indicates that the experimentation required to identify absolute inhibitors of cancer and hepatitis is not routine.

Quantity of Experimentation

Considering the breadth of the claims, the limited working examples provided, and the unpredictable nature of the art with respect to preventing disease, additional experimentation is required in order for one of skill in the art to be able to make and use the claimed polynucleotides with a reasonable expectation of success. For instance, polynucleotides other than poly-I and poly-C would have to be tested for there efficacy at treating diseases and

methods would have to be created in order to make these polynucleotides with 0.1% to 3% 2'-5' bonds, as there is no indication that the methods indicated could result in polynucleotides other than poly-I and poly-C having modified 2'-5' bonds. Furthermore, the polynucleotides encompassed by the claims would have to be tested for their ability to prevent any future occurrence of cancer or hepatitis in a subject. These experiments would take years of testing in culture systems, animal models and then in human trials without any guarantee of success.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the breadth of the claims, the limited working examples and guidance provided relative to the breadth of the claims, the state of the art and unpredictability with respect to compounds that can "prevent" disease, and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention to the full scope encompassed by the claims is undue.

Claim Objections

13. Claims 7, 8, 9, 12, 31 and 32 are objected to because of the following informalities:

Claim 7 recites the phrase "or sale thereof" in line 1. The word "sale" is believed to be a typographical error with the correct word being "salt". Claims 31 and 32 depend on claim 7 and are objected to for the same reason.

Claim 8 recites the phrase "or sale thereof" in line 2. The word "sale" is believed to be a typographical error with the correct word being "salt".

Claim 9 recites, "consisting of a combination of polyinosinic acid and polycytidylic acid, **of** polyadenylic..." [etc.] (emphasis added). The inclusion of the word "of" before each possible combination appears to be a typographical error. Deleting the inappropriate "**of**" from each of the possible combinations would obviate this rejection.

Claim 12 recites the word "cationoc" which is believed to be a typographical error with the correct word being "cationic".

Appropriate correction is required.

Miscellaneous

It is noted that a number of problems have arisen due to the misnumbering of claims and the renumbering of claims under CFR rule 1.132. Although it is not required, the Examiner would like to suggest to Applicants that one option which may help alleviate future problems would be to cancel all pending claims and then add the claims as new claims so that they are properly numbered and depend on the correct claim(s). Any new claims added should begin as number 33.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
July 13, 2003

DAVE T. NGUYEN
PRIMARY EXAMINER